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RCE 11/6/02

PATENT  
Attorney Docket No. 468267-00042/A-58762-9//RMS/RMK/CYQ

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

MEADE *et al.*

Serial No.: 09/306,749

Filed: 5/7/1999

For: *NUCLEIC ACID  
MEDIATED ELECTRON  
TRANSFER*

Group No. 1655

Examiner: S. Zitomer

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Box RCE, Commissioner for Patents, Washington, DC 20231

on:

Date:

Signature

*October 29, 2002*  
*Mary McFarland*  
Mary McFarland

**DECLARATION UNDER 37 C.F.R. § 1.132**

BOX RCE  
Commissioner for Patents  
Washington DC 20231

Sir:

I, Thomas J. Meade, do hereby declare as follows:

1. I received a Ph.D. degree in Inorganic Chemistry in 1985 from The Ohio State University. I am currently a Professor Of Chemistry; Biochemistry and Molecular and Cell Biology; and, Neurobiology and Physiology at Northwestern University. Prior to this, I was a Senior Research Faculty, Division of Biology and the Beckman Institute, California Institute of Technology.

2. Attached to this Declaration as Declaration Exhibit 1 is a copy of my curriculum vitae and a list of publications.

3. I am on the Scientific Advisory Board and a consultant for Clinic Micro Sensors, the exclusive licensee of this patent application.

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4. I have read and I understand the above-identified patent application, and the Office Action mailed July 29, 2002.

5. I understand the utility requirements as set forth under 35 U.S.C. §101 and MPEP § 2107-2107.03.

6. Based on my understanding, I believe that the described invention has a specific utility, that is the provision of modified nucleosides (i.e. nucleosides with "bulky" substituents" at the 2' position) for use as gene probes.

7. It is my opinion that a person of ordinary skill in the art would know that the utility of the present invention was to provide modified nucleosides for use as gene probes.

8. It is my opinion that a person of ordinary skill in the art of modified nucleosides did know that nucleosides with bulky substituents at the base were both available and routinely incorporated into nucleic acids, particularly using standard phosphoramidite chemistry.

9. It is my opinion that a person of ordinary skill in the art would appreciate that a nucleoside labeled with a bulky substituent at the 2' ribose position would be incorporated into nucleic acids both enzymatically and chemically. I base this opinion both on my training as a chemist and on a number of publications showing the routine chemistry of such reactions. For example, articles by Meade and Kayyem (1995) Angew. Chem. Int. Ed. Engl. 34: 352-353 (attached as Exhibit B), Yu et al. (2001) J. Org. Chem., 66:2937-2942 (attached as Exhibit C); Krider, et al (2001) Inorg. Chem., 40: 4002-4009 (attached as Exhibit D); Hwang and Greenberg, (1999) Organic Letters, 1: 2021-2024 (attached as Exhibit E); Hwang and Greenberg, (2001) J. Org. Chem., 66: 363-369

(attached as Exhibit F) Tsuneo, et al., (2000) Tetrahedron Letters, 41: 2605-2608

(attached as Exhibit G) describe modified nucleosides labeled with bulky substituents, such as fluorophores, transition metal complexes, etc., at the 2' position of ribose for incorporation into nucleic acids both enzymatically and chemically.

10. In addition, I would point out that nucleosides labeled with a bulky substituent at the 5' ribose position have also routinely been generated. For example, Modified nucleosides labeled at the 5' position with bulky substituents are also known. See for example, CA registry numbers 255852-09-6; 454464-20-1282543-35-5; 182005-99-8; 126139-47-7; and, 161016-72-4 (attached as Exhibit H).

11. I am aware of the Examiner's position that nucleosides modified at the 2' position of the ribose are not specifically described in the specification. However, as the Examiner has noted, Figure 4A and 4B show these structures. One of skill in the art, reading the description of using phosphoramidite chemistry on 2' amino modified nucleosides in the specification, would understand this chemistry to apply to modified nucleosides that further have the entire electron transfer moiety (ETM) attached at the 2' position.

12. With regard to this point, the specification outlines three components: the modification of nucleosides at the 2' position, the incorporation of metals and additional ligands at the 2' position, and the generation of phosphoramidite modified nucleosides as well as triphosphate modified nucleosides. It is my opinion that this disclosure shows the possession of doing these steps in a variety of orders, including adding an amino-modified nucleoside to a nucleic acid and then adding the metal, or adding the metal prior to incorporation into a nucleic acid.



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful, false statements may jeopardize the validity/enforceability of the application or any patent issued thereon.

Date: 10-28-02

Signed: Thomas J. Meade  
Thomas J. Meade, Ph.D.